CLAIMS

1. (Currently amended) A transgenic fly whose genome comprises a DNA sequence encoding a polypeptide comprising the Abeta portion of human APP wherein said DNA sequence encodes ~~Abeta40 (SEQ ID NO:1) or~~ Abeta42 (SEQ ID NO: 2), fused to a signal sequence, said DNA sequence operably linked to a tissue-specific expression control sequence; and expressing said DNA sequence, wherein expression of said DNA sequence results in said fly displaying an altered phenotype in tissue comprising neuronal cells.

2. (Original) The transgenic fly of claim 1 wherein said DNA sequence encodes Abeta42, and wherein said tissue specific expression control sequence comprises the eye-specific promoter GMR.

3. (Original) The transgenic fly of claim 2 wherein said expression of said DNA sequence results in said fly displaying the "rough eye" phenotype.

4. (Withdrawn) A transgenic fly whose genome comprises a DNA sequence encoding a polypeptide comprising the wild type C99 portion of human AP (SEQ. ID NO: 3) or C99 portion of human APP with the London Mutation (SEQ ID NO: 4), fused to a signal sequence, said DNA sequence operably linked to a tissue-specific expression control sequence; and expressing said DNA sequence, wherein expression of said DNA sequence results in said fly displaying an altered phenotype.

5. (Withdrawn) The transgenic fly of claim 4, wherein said DNA sequence encodes wild type C99, and wherein said tissue-specific expression control sequence comprises the UAS control element activated by Gal4 protein produced in the brain by the 7B-Gal4 transgene.

6. (Withdrawn) The transgenic fly of claim 5 wherein said expression of said DNA sequence results in said fly displaying a phenotype characterized as a locomotory defect.

7. (Withdrawn) The transgenic fly of claim 4, wherein said DNA sequence encodes either wild type C99 or C99 portion of human APP with the London Mutation, and wherein said tissue-specific expression control sequence is the UAS control element activated by Gal4 protein produced by the apterous-Gal4 transgene.

8. (Withdrawn) The transgenic fly of claim 7 wherein said expression of said DNA sequence results in said fly displaying the "concave wing" phenotype.

9. (Withdrawn) A method to identify genetic modifiers of the APP pathway, said method comprising:
(a) providing a transgenic fly whose genome comprises a DNA sequence encoding a polypeptide comprising the Abeta portion of human APP wherein said DNA sequence encodes Abeta40 (SEQ. ID NO:1) or Abeta42 (SEQ ID NO: 2), fused to a signal sequence, said DNA sequence operably linked to a tissue-specific expression control sequence; and expressing said DNA sequence, wherein expression of said DNA sequence results in said fly displaying an altered phenotype;
(b) crossing said transgenic fly with a fly containing a mutation in a known or predicted gene; and
(c) screening progeny of said crosses for flies that carry said DNA sequence and said mutation and display modified expression of the transgenic phenotype as compared to controls.

10. (Withdrawn) The method of claim 9 wherein said genetic modifier and/or its human homolog is a gene that affects the course of Alzheimer's Disease.

11. (Withdrawn) The method of claim 9 wherein said DNA sequence encodes Abeta42, and wherein said tissue specific expression control sequence comprises the eye-specific promoter GMR.

12. (Withdrawn) The method of claim 11 wherein said expression of said DNA sequence results in said fly displaying the "rough eye" phenotype.

13. (Withdrawn) A method to identify genetic modifiers of the APP pathway, said method comprising:
(a) providing a transgenic fly whose genome comprises a DNA sequence encoding a polypeptide comprising the wild type C99 portion of human APP (SEQ. ID NO:3) or C99 portion of human APP with the London Mutation (SEQ ID NO: 4), fused to a signal sequence, said DNA sequence operably linked to a tissue-specific expression control sequence; and expressing said DNA sequence, wherein expression of said DNA sequence results in said fly displaying an altered phenotype;
(b) crossing said transgenic fly with a fly containing a mutation in a known or predicted gene; and,

(c) screening progeny of said crosses for flies that carry said DNA sequence and said mutation and display modified expression of the transgenic phenotype as compared to controls.

14. (Withdrawn) The method of claim 13 wherein said genetic modifier and/or its human homolog is a gene that affects the course of Alzheimer's Disease.

15. (Withdrawn) The method of claim 13, wherein said DNA sequence encodes wild type C99 and wherein said tissue-specific expression control sequence comprises the UAS control element activated by Gal4 protein produced in the brain by the 7B-Gal4 transgene.

16. (Withdrawn) The method of claim 15 wherein expression of said DNA sequence results in said fly displaying a phenotype characterized by a locomotory defect.

17. (Withdrawn) The method of claim 13, wherein said DNA sequence encodes either wild type C99 or C99 portion of human APP with the London Mutation, and wherein said tissue-specific expression control sequence comprises the UAS control element activated by Gal4 protein produced by the apterous-Gal4 transgene.

18. (Withdrawn) The method of claim 17 wherein said expression of said DNA sequence results in said fly displaying the "concave wing" phenotype.

19. (Withdrawn) A method to identify targets for the development of therapeutics to treat, prevent or ameliorate conditions associated with abnormal regulation of the APP pathway said method comprising identifying the human homologs of the genetic modifiers identified according to the method of claim 9.

20. (Withdrawn) The method of claim 19 wherein said condition is Alzheimer's Disease.

21. (Withdrawn) The method of claim 19 further comprising identifying the human homologs of the genetic modifiers which map to the area on human chromosome 10 shown to have genetic linkage to Alzheimer's Disease.

22. (Withdrawn) A method to identify targets for the development of therapeutics to treat, prevent or ameliorate conditions associated with abnormal regulation of the APP pathway said method comprising identifying the human homologs of the genetic modifiers identified according to the method of claim 13.

23. (Withdrawn) The method of claim 22 wherein said condition is Alzheimer's Disease.

24. (Withdrawn) The method of claim 22 further comprising identifying the human homologs of the genetic modifiers which map to the area on human chromosome 10 shown to have genetic linkage to Alzheimer's Disease.

25. (Withdrawn) A method to identify targets for the development of therapeutics to treat, prevent or ameliorate conditions associated with abnormal regulation of the APP pathway, said method comprising identifying genes that are involved in the pathways regulated by the transcription factors encoded by the human sequences selected from the group consisting of hCP50765 (SEQ ID NO. 35) and hCP41313 (SEQ ID NO 15, SEQ ID NO17, SEQ ID NO 53).

26. (Withdrawn) The method of claim 25 wherein said condition is Alzheimer's Disease.

27. (Currently amended) A method to identify compounds useful for the treatment, ~~prevention~~ or amelioration of neurodegenerative conditions associated with abnormal regulation of the APP pathway comprising assaying for compounds that can modify the phenotypes induced by expression of Abeta, said method comprising:

(a) providing a transgenic fly whose genome comprises a DNA sequence encoding a polypeptide comprising the Abeta portion of human APP wherein said DNA sequence encodes ~~Abeta40 (SEQ. ID NO:1) or~~ Abeta42 (SEQ ID NO: 2), fused to a signal sequence, said DNA sequence operably linked to a tissue-specific expression control sequence; and expressing said DNA sequence, wherein expression of said DNA sequence results in said fly displaying an altered phenotype in tissue comprising neuronal cells;

(b) administering to said fly a candidate compound; and,

(c) assaying for changes in the phenotype of said fly of step (a) as compared to the phenotype of a fly of step (a) not administered the candidate compound.

28. (Original) The method of claim 27 wherein said condition is Alzheimer's Disease.

29. (Original) The method of claim 27 wherein said DNA sequence encodes Abeta42, and wherein said tissue specific expression control sequence is the eye-specific promoter GMR.

30. (Original) The method of claim 29 wherein said expression of said DNA sequence results in said fly displaying said altered phenotype referred to as the "rough eye" phenotype.

31. (Withdrawn) A method to identify compounds useful for the treatment, prevention or amelioration of conditions associated with abnormal regulation of the APP pathway comprising assaying for compounds that can modify the phenotypes induced by expression of C99, said method comprising:

(a) providing a transgenic fly whose genome comprises a DNA sequence encoding a polypeptide comprising the wild type C99 portion of human APP (SEQ. ID NO:3) or C99 portion of human APP with the London Mutation (SEQ ID NO: 4), fused to a signal sequence, said DNA sequence operably linked to a tissue-specific expression control sequence; and expressing said DNA sequence, wherein expression of said DNA sequence results in said fly displaying an altered phenotype;

(b) administering to said fly a candidate compound; and,

(c) assaying for changes in the phenotype of said fly of step (a) as compared to the phenotype of a fly of step (a) not administered the candidate compound.

32. (Withdrawn) The method of claim 31 wherein said condition is Alzheimer's Disease.

33. (Withdrawn) The method of claim 31, wherein said DNA sequence encodes wild type C99, and wherein said tissue-specific expression control sequence comprises the UAS control element activated by Gal4 protein produced in the brain by the 7B-Gal4 transgene.

34. (Withdrawn) The method of claim 33 wherein expression of said DNA sequence results in said fly displaying said altered phenotype characterized by a locomotory defect.

35. (Withdrawn) The method of claim 31, wherein said DNA sequence encodes either wild type C99 or C99 portion of human APP with the London Mutation, and wherein said tissue-specific expression control sequence comprises the UAS control element activated by Gal4 protein produced by the apterous-Gal4 transgene.

36. (Withdrawn) The method of claim 35 wherein said expression of said DNA sequence results in said fly displaying said altered phenotype referred to as the "concave wing" phenotype.

37. (Withdrawn) A method for identifying compounds useful for the treatment, prevention or amelioration of conditions associated with abnormal regulation of the APP pathway comprising

a) administering candidate compounds to an in vitro or in vivo model of Alzheimer's Disease; and,
b) assaying for changes in expression, protein level or protein activity of a homolog of a genetic modifier identified according to the method of claim 9 wherein altered expression, protein levels or protein activity of any one of said homologs compared to levels in a control to which a candidate compound has not been administered indicates a compound of therapeutic value.

38. (Withdrawn) A method for identifying compounds useful for the treatment, prevention or amelioration of conditions associated with abnormal regulation of the APP pathway comprising

a) administering candidate compounds to an in vitro or in vivo model of Alzheimer's Disease; and,
b) assaying for changes in expression, protein level or protein activity of a homolog of a genetic modifier identified according to the method of claim 13 wherein altered expression, protein levels or protein activity of any one of said homologs compared to levels in a control to which a candidate compound has not been administered indicates a compound of therapeutic value.

39. (Withdrawn) A method for identifying compounds useful for the treatment, prevention or amelioration of conditions associated with abnormal regulation of the APP pathway comprising

a) administering candidate compounds to an in vitro or in vivo model of Alzheimer's Disease; and,
b) assaying for changes in expression, protein level or protein activity of a homolog of a genetic modifier selected from the group consisting of those disclosed in Table 1 wherein altered expression, protein levels or protein activity of any one of said homologs compared to levels in a control to which a candidate compound has not been administered indicates a compound of therapeutic value.

40. (Withdrawn) The method of claim 39 wherein said human homolog is selected from the group consisting of hCP50765, (SEQ ID NO. 35), hCP41313 (SEQ ID NO 15, SEQ ID NO 17, SEQ ID NO 53), hCP33787 (SEQ ID NO 41) and hCP51594 (SEQ ID NO 43).

41. (Withdrawn) A method for the treatment, prevention or amelioration of conditions associated with abnormal regulation of the APP pathway comprising administering to a subject in need thereof a therapeutically effective amount of a substance that inhibits or promotes the expression and/or function of any one or more of the genes or encoded polypeptides of the human homologs of a genetic modifier identified according to the method of claim 9.

42. (Withdrawn) The method of claim 41 wherein said substance is selected from the group consisting of: compounds, triple helix DNA, antisense oligonucleotides, double stranded RNA molecules and ribozymes, and wherein said substances are designed to inhibit expression of any one or more of the human homologs of said genetic modifiers.

43. (Withdrawn) The method of claim 41 wherein said substance comprises any one or more antibodies and/or fragments thereof directed to the polypeptide encoded by any one or more of the human homologs of said genetic modifiers.

44. (Withdrawn) The method of claim 41 wherein said conditions include Alzheimer's Disease.

45. (Withdrawn) A method for the treatment, prevention or amelioration of conditions associated with abnormal regulation of the APP pathway comprising administering to a subject in need thereof a therapeutically effective amount of a substance that inhibits or promotes the expression and/or function of any one or more of the genes or encoded polypeptides of the human homologs of a genetic modifier identified according to the method of claim 13.

46. (Withdrawn) The method of claim 45 wherein said substance is selected from the group consisting of: compounds, triple helix DNA, antisense oligonucleotides, double stranded RNA molecules and ribozymes, and wherein said substances are designed to inhibit expression of any one or more of the human homologs of said genetic modifiers.

47. (Withdrawn) The method of claim 45 wherein said substance comprises any one or more antibodies and/or fragments thereof directed to the polypeptide encoded by any one or more of the human homologs of said genetic modifiers.

48. (Withdrawn) The method of claim 45 wherein said conditions include Alzheimer's Disease.

49. (Withdrawn) A method for the treatment, prevention or amelioration of conditions associated with abnormal regulation of the APP pathway comprising administering to a subject in need thereof a therapeutically effective amount of a substance that inhibits or promotes the expression and/or function of any one or more of the genes or encoded polypeptides of the human homologs of a genetic modifier wherein said genetic modifiers are selected from the group consisting of those disclosed in Table 1.

50. (Withdrawn) The method of claim 49 wherein said substance is selected from the group consisting of: compounds, triple helix DNA, antisense oligonucleotides, double stranded RNA molecules and ribozymes, and wherein said substances are designed to inhibit expression of any one or more of the human homologs of said genetic modifiers.

51. (Withdrawn) The method of claim 49 wherein said substance comprises any one or more antibodies and/or fragments thereof directed to the polypeptide encoded by any one or more of the human homologs of said genetic modifiers.

52. (Withdrawn) The method of claim 49 wherein said human homolog is selected from the group consisting of hCP50765, (SEQ ID NO. 35), hCP41313 (SEQ ID NO 15, SEQ ID NO 17 , SEQ ID NO 53), hCP33787 (SEQ ID NO 41) and hCP51594 (SEQ ID NO 43).

53. (Withdrawn) The method of claim 49 wherein said conditions include Alzheimer's Disease.

54. (Withdrawn) A method for the treatment, prevention or amelioration of conditions associated with abnormal regulation of the APP pathway comprising administering to a subject in need thereof a pharmaceutical composition comprising a therapeutically effective amount of a substance that inhibits or promotes the expression and/or function of any one or more of the genes or encoded polypeptides of the human homologs of a genetic modifier identified according to the method of claim 9.

55. (Withdrawn) The method of claim 54 wherein said pharmaceutical composition comprises a therapeutically effective amount of a substance selected from the group consisting of: compounds, triple helix DNA, antisense oligonucleotides, double stranded RNA molecules and ribozymes, and wherein said substances are designed to inhibit expression of any one or more of the human homologs of said genetic modifiers.

56. (Withdrawn) The method of claim 54 wherein said pharmaceutical composition comprises a therapeutically effective amount of an antibody or antibodies and/or fragments thereof directed to the polypeptide encoded by any one or more of the human homologs of said genetic modifiers.

57. (Withdrawn) The method of claim 54 wherein said conditions include Alzheimer's Disease.

58. (Withdrawn) A method for the treatment, prevention or amelioration of conditions associated with abnormal regulation of the APP pathway comprising administering to a subject in need thereof a pharmaceutical composition comprising a therapeutically effective amount of a substance that inhibits or promotes the expression and/or function of any one or more of the genes or encoded polypeptides of the human homologs of a genetic modifier identified according to the method of claim 13.

59. (Withdrawn) The method of claim 58 wherein said pharmaceutical composition comprises a therapeutically effective amount of a substance selected from the group consisting of: compounds, triple helix DNA, antisense oligonucleotides, double stranded RNA molecules and ribozymes, and wherein said substances are designed to inhibit expression of any one or more of the human homologs of said genetic modifiers.

60. (Withdrawn) The method of claim 58 wherein said pharmaceutical composition comprises a therapeutically effective amount of an antibody or antibodies and/or fragments thereof directed to the polypeptide encoded by any one or more of the human homologs of said genetic modifiers.

61. (Withdrawn) The method of claim 58 wherein said conditions include Alzheimer's Disease.

62. (Withdrawn) A method for the treatment, prevention or amelioration of conditions associated with abnormal regulation of the APP pathway comprising administering to a subject in need thereof a pharmaceutical composition comprising a therapeutically effective amount of a substance that inhibits or promotes the expression and/or function of any one or more of the genes or encoded polypeptides of the human homologs selected from the group consisting of those disclosed in Table 1.

63. (Withdrawn) The method of claim 62 wherein said pharmaceutical composition comprises a therapeutically effective amount of a substance selected from the group

consisting of: compounds, triple helix DNA, antisense oligonucleotides, double stranded RNA molecules and ribozymes, and wherein said substances are designed to inhibit expression of any one or more of the human homologs of said genetic modifiers.

64. (Withdrawn) The method of claim 62 wherein said pharmaceutical composition comprises a therapeutically effective amount of an antibody or antibodies and/or fragments thereof directed to the polypeptide encoded by any one or more of the human homologs of said genetic modifiers.

65. (Withdrawn) The method of claim 62 wherein said conditions include Alzheimer's Disease.

66. (Withdrawn) The method of claim 62 wherein said human homolog is selected from the group consisting of hCP50765, (SEQ ID NO. 35), hCP41313 (SEQ ID NO 15, SEQ ID NO 17, SEQ ID NO 53), hCP33787 (SEQ ID NO 41) and hCP51594 (SEQ ID NO 43).

67. (Withdrawn) The method of claim 66 wherein said conditions include Alzheimer's Disease.

68. (Withdrawn) A pharmaceutical composition comprising a substance that inhibits or promotes the expression and/or function of any one or more of the genes or encoded polypeptides of the human homologs of a genetic modifier identified according to the method of claim 9 in an amount effective to prevent, treat or ameliorate a condition associated with abnormal regulation of the APP pathway in a subject in need thereof.

69. (Withdrawn) The pharmaceutical composition of claim 68 comprising a substance selected from the group consisting of: compounds, triple helix DNA, antisense oligonucleotides, double stranded RNA molecules and ribozymes, and wherein said substances are designed to inhibit expression of any one or more of the human homologs of said genetic modifiers.

70. (Withdrawn) The pharmaceutical composition of claim 68 comprising an antibody or antibodies and/or fragments thereof directed to the polypeptide encoded by any one or more of the human homologs of said genetic modifiers.

71. (Withdrawn) The pharmaceutical composition of claim 68 wherein said condition is Alzheimer's Disease.

72. (Withdrawn) A pharmaceutical composition comprising a substance that inhibits or promotes the expression and/or function of any one or more of the genes or encoded polypeptides of the human homologs of a genetic modifier identified according to the method of claim 13 in an amount effective to prevent, treat or ameliorate a condition associated with abnormal regulation of the APP pathway in a subject in need thereof.

73. (Withdrawn) The pharmaceutical composition of claim 72 comprising a substance selected from the group consisting of: compounds, triple helix DNA, antisense oligonucleotides, double stranded RNA molecules and ribozymes, and wherein said substances are designed to inhibit expression of any one or more of the human homologs of said genetic modifiers.

74. (Withdrawn) The pharmaceutical composition of claim 72 comprising an antibody or antibodies and/or fragments thereof directed to the polypeptide encoded by any one or more of the human homologs of said genetic modifiers.

75. (Withdrawn) The pharmaceutical composition of claim 72 wherein said condition is Alzheimer's Disease.

76. (Withdrawn) A pharmaceutical composition comprising a substance that inhibits or promotes the expression and/or function of any one or more of the genes or encoded polypeptides of the human homologs of a genetic modifier selected from the group consisting of those disclosed in Table 1 in an amount effective to prevent, treat or ameliorate a condition associated with abnormal regulation of the APP pathway in a subject in need thereof.

77. (Withdrawn) The pharmaceutical composition of claim 76 comprising a substance selected from the group consisting of: compounds, triple helix DNA, antisense oligonucleotides, double stranded RNA molecules and ribozymes, and wherein said substances are designed to inhibit expression of any one or more of the human homologs of said genetic modifiers.

78. (Withdrawn) The pharmaceutical composition of claim 76 comprising an antibody or antibodies and/or fragments thereof directed to the polypeptide encoded by any one or more of the human homologs of said genetic modifiers.

79. (Withdrawn) The pharmaceutical composition of claim 76 wherein said condition is Alzheimer's Disease.

80. (Withdrawn) The pharmaceutical composition of claim 76 wherein said human homolog is selected from the group consisting of hCP50765, (SEQ ID NO. 35), hCP41313 (SEQ ID NO 15, SEQ ID NO 17, SEQ ID NO 53), hCP33787 (SEQ ID NO 41) and hCP51594 (SEQ ID NO 43).

81. (Withdrawn) The pharmaceutical composition of claim 80 wherein said condition is Alzheimer's Disease.

82. (Withdrawn) A method to treat, prevent or ameliorate conditions associated with abnormal regulation of the APP pathway comprising:

(a) assaying for mRNA and/or protein levels of a human homolog of a genetic modifier identified according to the method of claim 9 in a subject; and,
(b) administering to a subject with abnormal mRNA and/or protein levels compared to controls a substance in an amount sufficient to treat or ameliorate the pathological effects of said condition.

83. (Withdrawn) The method of claim 82 wherein said condition is Alzheimer's Disease.

84. (Withdrawn) A method to treat, prevent or ameliorate conditions associated with abnormal regulation of the APP pathway comprising:

a) assaying for mRNA and/or protein levels of a human homolog of a genetic modifier identified according to the method of claim 13 in a subject; and,
b) administering to a subject with abnormal mRNA and/or protein levels compared to controls a substance in an amount sufficient to treat or ameliorate the pathological effects of said condition.

85. (Withdrawn) The method of claim 84 wherein said condition is Alzheimer's Disease.

86. (Withdrawn) A method to treat, prevent or ameliorate conditions associated with abnormal regulation of the APP pathway comprising:

a) assaying for mRNA and/or protein levels of a human homolog of a genetic modifier selected from the group consisting of those disclosed in Table 1 in a subject; and,
b) administering to a subject with abnormal mRNA and/or protein levels compared to controls a substance in an amount sufficient to treat or ameliorate

the pathological effects of said condition.

87. (Withdrawn) The method of claim 86 wherein said condition is Alzheimer's Disease.

88. (Withdrawn) The method of claim 86 wherein said human homolog is selected from the group consisting of hCP50765, (SEQ ID NO. 35), hCP41313 (SEQ ID NO 15, SEQ ID NO , SEQ ID NO 53), hCP33787 (SEQ ID NO 41) and hCP51594 (SEQ ID NO 43).

89. (Withdrawn) The method of claim 88 wherein said condition is Alzheimer's Disease.

90. (Withdrawn) A diagnostic kit for detecting mRNA levels and/or protein levels of a human homolog of a genetic modifier identified according to the method of claim 9 in a biological sample, said kit comprising:

(a) a polynucleotide of a human homolog of a genetic modifier or a fragment thereof;
(b) a nucleotide sequence complementary to that of (a);
(c) a polypeptide of a human homolog of a genetic modifier, or a fragment thereof; or
(d) an antibody to said polypeptide

wherein components (a), (b), (c) or (d) may comprise a substantial component.

91. (Withdrawn) A diagnostic kit for detecting mRNA levels and/or protein levels of a human homolog of a genetic modifier identified according to the method of claim 13 in a biological sample, said kit comprising:

(a) a polynucleotide of a human homolog of a genetic modifier or a fragment thereof;
(b) a nucleotide sequence complementary to that of (a);
(c) a polypeptide of a human homolog of a genetic modifier, or a fragment thereof; or
(d) an antibody to said polypeptide

wherein components (a), (b), (c) or (d) may comprise a substantial component.

92. (Withdrawn) A diagnostic kit for detecting mRNA levels and/or protein levels of a human homolog of a genetic modifier selected from the group consisting of those disclosed in Table 1 in a biological sample, said kit comprising:

(a) a polynucleotide of a human homolog of a genetic modifier or a fragment thereof;

(b) a nucleotide sequence complementary to that of (a);

(c) a polypeptide of a human homolog of a genetic modifier, or a fragment thereof; or

(d) an antibody to said polypeptide

wherein components (a), (b), (c) or (d) may comprise a substantial component.

93. (Withdrawn) The diagnostic kit of claim 92 wherein said human homolog is selected from the group consisting of hCP50765, (SEQ ID NO. 35), hCP41313 (SEQ ID NO 15, SEQ ID NO 17, SEQ ID NO 53), hCP33787 (SEQ ID NO 41) and hCP51594 (SEQ ID NO 43).

94. (Withdrawn) A method to diagnose subjects suffering from conditions associated with abnormal regulation of the APP pathway comprising measuring the mRNA level and/or the level or activity of polypeptides encoded by any one or more of the human homologs of a genetic modifier identified according to the method of claim 9, in a biological sample from a subject, wherein an abnormal level relative to the level thereof in a control subject is diagnostic of said condition.

95. (Withdrawn) The method of claim 94 wherein said conditions include Alzheimer's Disease.

96. (Withdrawn) A method to diagnose subjects suffering from conditions associated with abnormal regulation of the APP pathway comprising measuring the mRNA level and/or the level or activity of polypeptides encoded by any one or more of the human homologs of a genetic modifier identified according to the method of claim 13, in a biological sample from a subject, wherein an abnormal level relative to the level thereof in a control subject is diagnostic of said condition.

97. (Withdrawn) The method of claim 96 wherein said conditions include Alzheimer's Disease.

98. (Withdrawn) A method to diagnose subjects suffering from conditions associated with abnormal regulation of the APP pathway comprising measuring the mRNA level and/or the level or activity of polypeptides encoded by any one or more of the human homologs of a genetic modifier selected from the group consisting of those disclosed in Table 1, in a biological sample from a subject, wherein an abnormal level relative to the level thereof

in a control subject is diagnostic of said condition.

99. (Withdrawn) The method of claim 98 wherein said conditions include Alzheimer's Disease.

100. (Withdrawn) The method of claim 98 wherein said human homolog is selected from the group consisting of hCP50765, (SEQ ID NO. 35), hCP41313 (SEQ ID NO 15, SEQ ID NO 17, SEQ ID NO 53), hCP33787 (SEQ ID NO 41) and hCP51594 (SEQ ID NO 43).

101. (Withdrawn) The method of claim 100 wherein said conditions include Alzheimer's Disease.

102. (Withdrawn) A method to treat, prevent or ameliorate conditions associated with abnormal regulation of the APP pathway comprising introducing nucleic acids encoding any one or more of the human homologs of a genetic modifier identified according to the method of claim 9 into one or more tissues of a subject in need thereof resulting in expression and/or secretion by cells within the subject of one or more proteins encoded by the nucleic acids.

103. (Withdrawn) The method of claim 102 wherein said conditions include Alzheimer's Disease.

104. (Withdrawn) A method to treat, prevent or ameliorate conditions associated with abnormal regulation of the APP pathway comprising introducing nucleic acids encoding any one or more of the human homologs of a genetic modifier identified according to the method of claim 13 into one or more tissues of a subject in need thereof resulting in expression and/or secretion by cells within the subject of one or more proteins encoded by the nucleic acids.

105. (Withdrawn) The method of claim 104 wherein said conditions include Alzheimer's Disease.

106. (Withdrawn) A method to treat, prevent or ameliorate conditions associated with abnormal regulation of the APP pathway comprising introducing nucleic acids encoding any one or more of the human homologs of a genetic modifier selected from the group consisting of those disclosed in Table 1 into one or more tissues of a subject in need thereof resulting in expression and/or secretion by cells within the subject of one or more proteins encoded by the nucleic acids.

107. (Withdrawn) The method of claim 106 wherein said conditions include Alzheimer's Disease.

108. (Withdrawn) The method of claim 106 wherein said human homolog is selected from the group consisting of hCP50765, (SEQ ID NO. 35), hCP41313 (SEQ ID NO 15, SEQ ID NO 17, SEQ ID NO 53), hCP33787 (SEQ ID NO 41) and hCP51594 (SEQ ID NO 43).

109. (Withdrawn) The method of claim 108 wherein said conditions include Alzheimer's Disease.

110. (New) The transgenic fly of claim 1 wherein said expression of said DNA sequence results in said fly displaying an altered phenotype in a tissue selected from the group consisting of eye, wing, notum, brain, CNS and PNS.

111. (New) The transgenic fly of claim 30 wherein said expression of said DNA sequence results in said fly displaying an altered phenotype in a tissue selected from the group consisting of eye, wing, notum, brain, CNS and PNS

RESPONSE

Claims 1-3 and 27-30 are pending the application. Pursuant to the restriction requirement, claims 4-26 and 31-33 have been withdrawn from further consideration.

Support for amended claims 1 and 27 can be found in the specification at page, 52, lines 7-8. Support for newly added claims 109 and 110 can be found in the specification at page 16, lines 1-8, and page 52 lines 7-8. No new matter has been added.

Rejection under 35 USC 112, first paragraph

Claims 1-3 and 27-30 stand rejected under 35 USC 112, first paragraph because the specification allegedly does not enable a person skilled in the art to make or use the invention commensurate in scope with these claims. Applicants respectfully traverse the rejection.

Specifically, the Examiner states the specification enables a transgenic fly comprising a DNA sequence encoding Abeta42 operably linked to an eye-specific expression control sequence displaying a rough eye phenotype and method of using said fly to identify compounds that treat or ameliorate neural degeneration or symptoms of Alzheimers Disease. However, the Examiner contends the specification:

> ...does not reasonably provide enablement for said fly wherein the DNA sequence encoding Abeta42 is operably linked to any tissue-specific expression control sequence wherein expression of said DNA sequence results in said fly displaying any phenotype or a method of using said fly to identify compounds that affect any condition or prevent any condition.

In support of this, the Examiner cites multiple references published from 1991 to 1997 that allegedly describes the unpredictability of the state of the art of transgenic animals (see page 5, second paragraph of the Office Action) at the time of filing.

The state of transgenic art in 2001 when Applicants filed their invention, has developed significantly making techniques in the transgenic field routine and conventional. In the specification, Applicants use conventional methods of producing transgenic Drosophila as provided:

> "...P element mediated transformation in Drosophila: A practical approach (ed. D.B. Roberts), pp175-197 IRL Press, Oxford, UK). The EP element technology refers to a binary system, utilizing the yeast Gal4 transcriptional activator, which is used to ectopically regulate the transcription of endogenous Drosophila genes. This technology is described in: Brand and Perrimon, 1993. Targeted gene expression as a means of altering cell fates and generating dominant phenotypes. Development 118, pp 401-415 and in Rorth et al, 1998, Systematic gain-of-function genetics in Drosophila. Development, 125(6), pp1049-1057.: (specification page 15, lines 13-22)

For the Examiner's convenience, Applicants attach herewith a copy of the Brand and Perrimon reference as Exhibit A. Specifically, Brand and Perrimon teach:

> ...a vector that, depending upon its genomic site of integration, can direct expression of GAL4 in a wide range of patterns in embryos, larvae and adults. This eliminates the need to link numerous different promoters to the GAL4 gene, and allows expression in novel patterns from enhancers that have not yet been described....It is possible, then: (1) to subclone any sequence behind GAL4 binding sites; (2) to activate that target gene only within cells where GAL4 is expressed and (3) to observe the effect of this aberrant expression on development.

Brand, et al. describe detailed methods of creating transgenic Drosophila and further provide figures (see, e.g. Figure 3) showing various phenotypes expressed. Thus the method of Brand and Perrimon is one example to which the skilled artisan can refer and follow to readily create and identify, without undue experimentation, transgenic Drosophila comprising tissue specific expression controls sequences and generation of altered phenotypes.

In conjunction with the teachings of Brand and Perrimon and in addition to established Drosophila literature, the specification directs one of skill in the art to access free, public databases, such as Flybase, which provides annotations and curation of experimental data compiled from the research community. Such electronic database provides genetic information including expression properties of transcripts and proteins in organ systems (e.g. the nervous system), physical maps and clone-based sequences encompassed within the euchromatic Drosophila genome. From this comprehensive list, one of skill in the art can readily query and select a target, tissue-specific sequence, phenotype or organ which provides an altered phenotype in a fly model.

Consequently, Applicants submit that statements contained in the Office Action regarding the unpredictability of phenotypes in transgenic animal technology is unfounded and in contradiction to the recent reports and public databases detailing genetic information available to produce specific phenotypic expression.

The Examiner further states in item (1):

> The specification fails to enable using any tissue-specific expression control sequences other than an eye-specific expression control sequence.

and item (2):

> One of skill in the art would not know how to use a transgenic fly exhibiting a phenotype other than rough eye. Furthermore, based on the unpredictability of phenotype as set forth by state of art described above, it would require undue experimentation for one of skill in the art to determine how to make the claimed fly such that it exhibits any altered phenotype other than rough eye phenotype.

However, to the contrary, the specification teaches:

> The fused DNA sequence are operably linked to tissue-specific expression control sequences such as promoter regions or upstream activating sequences (UAS) depending on the expression system utilized. These expression control sequences include those that are specific for neural tissue and include organs such as the eye, wing, notum, brain,

> CNS and PNS. Under the control of these tissue specific control sequences, encoded peptides are transcribed to form mRNA which is translated into detectible levels of beta amyloid or C99 peptide and which causes altered phenotypes in the flies.

Applicants submit the specification fully enables the claimed transgenic fly and method of identify compounds using a transgenic fly, such as eye, wing, notum, brain, CNS and PNS organs in Drosophila which comprise neuronal cells. One of skill in the art guided by the specification, available literature as well as information provided by various Drosophila consortiums has the ability and knowledge to select a specific tissue expression control sequence commonly used in the art to generate a transgenic fly in which overexpression of Abeta42 produces visible defects or altered phenotypes as compared to control flies. Applicants submit, the importance of the invention lies not only in a specific phenotype (eye or wing) produced but in the generation and development of flies that produce an abnormal phenotype as a result of overexpression of beta amyloid proteins. The flies of the invention can then be used to identify genes acting in the beta amyloid pathway that produces such abnormal phenotypes to identify therapeutics to treat or reverse the abnormalities produced by such genes.

However, to facilitate prosecution, while not necessarily agreeing with the grounds for this rejection, claims 1 and 27 have been amended to recite that the altered phenotype is displayed in a "tissue comprising neuronal cells"..

Regarding the Examiners statement in item (3):

> The specification does not teach any phenotype other than neurodegeneration that is associated with abnormal regulation of the APP pathway. Therefore one of skill in the art would not know how to carry out the method of claim 27 wherein the condition is any condition associated with abnormal regulation of APP pathway other than neurodegeneration...

and in item (4):

> The specification is not enabling for identifying a compound that prevents a condition.

Applicants disagree that one of skill in the art would not know how to carry out the method of claim 27 for the reasons stated above. However, in order to facilitate prosecution and while not necessarily agreeing with the grounds for this rejection, claim 27 has been amended to further recite the condition associated with abnormal regulation of the APP pathway is a "neurodegenerative condition" and delete recitation of the term "prevention".

Accordingly, Applicants submit that, in light of the information contained in the present specification and in view of the level of skill in the art of transgenic animals and gene expression, it would not require undue experimentation to practice the claimed invention. In view of the above, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-3 and 27-30 under 35 USC 112, first paragraph.